IN THE DRAWINGS:

Accompanying this Amendment are the attached sheets of drawings that include changes to FIGS. 4, 8, and 10. These sheets, which include FIGS. 4, 8, and 10, replace the original sheets including FIGS. 1 through 21.

FIGS. 4, 8, and 10 have been amended herein. Specifically, FIGS. 4, 8, and 10 have been revised to delete the term "treatbin" from each figure. No new matter has been added.

REMARKS

The Office Action mailed June 7, 2005 has been received and reviewed. The application is to be amended as previously set forth. All amendments are made without prejudice or disclaimer. The amendments do not surrender any scope of any claim as originally filed. No new matter has been entered. Support for the amendment can be found in paragraph [0005] among other places. Claims 1-11 and 15-24 are pending in the application. Claims 1-11 and 15-21 stand rejected. Reconsideration is respectfully requested.

1. Claims 1-21 and 35 U.S.C. § 112, 1st ¶

Claims 1-21 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly lacking enablement and failing to comply with the written description requirement. Specifically, it was thought that the specification does not reasonably provide enablement for a method of administering IFN type-I, or functional parts, derivatives, and analogues of IFN type-I. The Examiner asserts that IFN type-1 encompasses a number of molecules and that the disclosure only supports IFN-β. Regarding the "functional part," the Examiner asserts that what makes up the part of IFN-β responsible for post-ischaemic activity is not disclosed or known in the art. Regarding derivatives and/or analogues, the Examiner asserts that applicants have not further defined what these molecules may encompass. The Examiner further asserts that in some situations the alteration of a single amino acid or nucleotide in a protein can alter the function or activity of a protein, and therefore, that could be the case with IFN-β. It is further asserted that claims 1-21 insufficiently indicate the amount of IFN to be administered. Regarding claim 11, the Examiner asserts that claim 11 reads on preventing cell death in a single cell as well preventing cell death in every cell. Regarding claim 12, the Examiner asserts that the claim does not indicate any particular etiology. The rejection based upon the written description requirement was grounded on the same reasoning as the enablement rejection. Specifically, it was thought that it was not clear what region of the protein was responsible for activity. It was also thought that one of ordinary skill in the art cannot envision the detailed chemical structure of the encompassed genus of polypeptides to be used in the claimed invention. Applicants respectfully traverse these rejections.

M.P.E.P § 2164.02 provides that "[p]roof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation."

Applicants respectfully submit that interferons are a long studied group of proteins of which much is known. One of ordinary skill in the art is well aware of the functional parts, suitable derivatives, and analogues of IFN type-I. Members of the IFN type-I family include 13 IFN-α subtypes, IFN-β, IFN-ω, and IFN-τ. Antiviral activity led to the name 'interferon' and still serves to define the unit of IFN activity. However, type-1 IFNs also have anti-proliferative, immunomodulatory, and other activities. All human type-1 IFN genes are clustered in the same chromosomal region, on the short arm of chromosome 9. A dendogram constructed on basis of a Njplot profile revealed that IFN-α subtypes, IFN-β, IFN-ω, and IFN-τ fall into one cluster, indicating that all type-1 IFNs are closely related. Type-1 IFNs differ, with respect to N-glycosylation sites, with those present in IFN-β. However, the sugar moiety was found to be neither structurally nor functionally relevant. All type-1 IFNs are acid-stable to pH 2 and heat-stable. Three-dimensional models suggest that the globular structure of type-1 IFNs consists of a bundle of five alpha-helices, which form two polypeptide domains. Disulfide bond Cys29-Cys139 stabilizes both domains in a bioactive configuration. The IFN molecule exerts its functional entity only as an organic polypeptide complex and therefore molecular fragments apparently lack biological activity. All type-1 IFNs have overlapping functions and bind to the same cell surface receptor, a fact implying a high structural conservation of their receptor-binding areas. All type-1 interferons (interferon-alpha, interferon beta, interferon-omega, hybrids and consensus version thereof) share a common receptor through which their effects are mediated (*i.e.*, composed of the alpha/beta interferon receptor IFNAR-1 and IFNAR-2 chains (Uze et al., 1990, Cell 60, 225-234; Novick et al., 1994, Cell 77, 391-400; Domanski et al., 1995, J. Biol. Chem. 270, 21606-21611). These facts are all well-known to those of ordinary skill in the art. Therefore, not only is the disclosure enabling for IFN-β, but also for IFN type-I.

Additionally, one of ordinary skill in the art can rely of a large body of interferon art to produce many different derivatives or analogues of interferon-β. It is therefore respectfully

submitted that one of ordinary skill in the art is not presented with an undue burden for selecting a suitable analogue. Below are specific examples of IFN-β derivatives and analogues; however, based upon the above reasoning these examples apply to the IFN type-I genus as well.

For instance, applicants submit that a number of recombinant IFN-β proteins have been approved for the treatment of multiple sclerosis, a glycosylated form with the predicted natural amino acid sequence (IFN-β-1a) and a non-glycosylated form that has a Met-1 deletion and a Cys-17 to Ser mutation (IFN-β-1b). This latter IFN-β protein is also called rIFN-β-Ser or Betaseron. IFN-β-lb is both a derivative of human IFN-β, where serine was genetically engineered to substitute for cysteine at position 17 and is produced in *E. coli*, and a part of human IFN-β, *i.e.*, a part without the glycosylation of human IFN-β. The site-specific substitution was made to obtain a product that is more stable upon storage. IFN-β-lb has been shown to have the same panel of biological activities as glycosylated native IFN-β and IFN-β-1a. (Runkel et al. 1998). Thus, non-glycosylated IFN-β is both a functional derivative and a functional part of IFN-β.

Applicants respectfully submit that interferon alfacon-1 (also referred to as "consensus IFN") is a synthetic recombinant type-1 IFN developed by comparing the amino acid sequences of several natural IFN-α subtypes and assigning the most frequently observed amino acid in each corresponding position to generate a consensus molecule. Consensus IFN binds with high affinity to the type-1 IFN receptor and has greater biological activity than naturally occurring IFN-alpha subtypes. (Koyama et al. 1999). One of ordinary skill in the art can thus produce interferons with no counterpart in nature. It is therefore respectfully submitted that one of ordinary skill in the art knows how to produce analogues of IFN-β. Therefore, one of ordinary skill in the art knows how to produce derivatives and analogues of IFN type-I.

The rejection of claims 1-21 based upon insufficient indication of the amount of IFN to be administered has been cured by the amendment to claims 1, 9-11, and 15.

The rejection with respect to claim 11 relating to "at least in part preventing cell death" is rendered moot with the amendment to claim 11.

Claims 12-14 have been cancelled rendering the rejection thereof moot.

Regarding enablement, the above explanation clearly shows that a person of ordinary skill

in the art would be able to practice the invention commensurate in scope with the claims without undue experimentation. Therefore, claims 1-11 and 15-21 are enabled.

Applicants respectfully submit that the specification provides adequate written description for a method of administering a functional part, derivative, and/or analogues of IFN type-1. The Examiner is referred to paragraph [0053] of the specification which refers to the work of Viscomi GC (1997). This is a direct reference to art for structure and activity of type-I interferons relating to the present invention. Applicants note that the structure of claimed compounds is not required to satisfy the written description requirement. M.P.E.P. § 2163(a)(ii) provides that "[t]he written description requirement for a claimed genus may be satisfied by . . . functional characteristics coupled with a known or disclosed correlation between function and structure . . . sufficient to show the applicant was in possession of the invention." The above discussion clearly shows functional derivatives of IFN-β and a known method for developing an analogue. Given the abundant knowledge in the interferon art, applicants are clearly in possession of the claimed uses of IFN type-I, a functional part, derivative, and/or analogue thereof.

Therefore, applicants have satisfied the written description requirement.

2. Claims 1-21 and 35 U.S.C. § 112, 2nd ¶

Claims 1-21 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being incomplete for omitting essential steps. Claim 12 is rejected as being indefinite. Regarding the omitted steps specifically, it was thought that the omitted steps are: how outcomes are to be measured and what is the correlation between the measured variable and the claimed method so that the measured variable may be controlled. Applicants respectfully traverse these rejections.

Applicants respectfully submit that hypoxia/ischaemia (H/I) related inflammation is a problem in a variety of human diseases (paragraphs [0004], [0006], and [0008]), one of which is traumatic brain injury (paragraph [0007]). Other situations where H/I related inflammation occurs are: a person has not been able to breathe oxygen for a limited amount of time (paragraph [0007]) and in other cases. Physicians are familiar with hypoxia and ischaemia situations. Physicians are also the appropriate person to identify the presence of a disorder in which this

resistance occurs. He or she will be able to do that as there are methods available to identify patients with hypoxia or ischaemia. Physicians will furthermore be able to establish whether the condition of the a patient improves. The specification further provides adequate guidance for the person skilled in the art to arrive at an effective dose, both in the examples and in the description (paragraphs [0057]-[0059]). Additionally, for a step to be "essential" it must be "disclosed to be essential to the invention as described in the specification or in other statements of record." *See* M.P.E.P. § 2173.01. The Examiner has not provided any "statements of record" that the above referenced steps are essential to the claimed invention. Therefore, claims 1-21 are not incomplete for omitting essential matter.

Regarding indefiniteness, claim 12 has been cancelled rendering the rejection thereof moot.

3. Claims 1-21 and 35 U.S.C. § 103(a)

Claims 1-21 stand rejected under 35 U.S.C. § 103(a) as assertedly being obvious in light of Wee Yong *et al.* in view of Boyle *et al.* and Saikumar *et al.* Specifically, it was thought that Wee Yong *et al.* teaches that IFN-β, a type-I interferon, is immunosuppressive and possesses various anti-inflammatory properties, but that Wee Yong *et al.* does not teach the use of IFN-β to treat H/I related inflammation. It was also thought that Boyle *et al.* teaches that H/I related inflammation (assuming this is what the Examiner intended) is an inflammatory process and anti-adhesion molecule therapy is effective. It was also thought that Saikumar *et al.* teaches that the inflammatory process is responsible for cell death as a result of H/I. The Examiner asserts that it would have been obvious to use IFN-β, a type-I interferon, to treat H/I related blood flow resistance, including treating the resulting cell death, because H/I related blood flow resistance and cell death are inflammatory process and IFN-β has anti-inflammatory properties. The Examiner also thought that there is no indication in the art that H/I is markedly different in various parts of an organism. The Examiner asserted that therefore IFN-β would be expected to be effective in the brain, heart, limbs, or transplanted organs because the results of H/I are the same in those organs. Applicants respectfully traverse this rejection.

Applicants respectfully submit that interferon has many properties of which an anti-

inflammatory property is only one. Even if one would decide that an anti-inflammatory property is an essential quality for a method for the treatment of H/I related inflammation, one's choice would not likely be interferon. There are very many anti-inflammatory drugs, of which many have a far stronger anti-inflammatory effect then interferon. The mere fact that a compound has an anti-inflammatory effect does not make it suitable for a method of the invention.

For example, it is well known in the art that corticosteroids are among the most potent and widely used anti-inflammatory drugs. Members of this class of drugs would be a much more likely choice if one had the intention to treat the putative inflammatory component of the cascade leading to cell death after an H/I related inflammation. Several members of this well-known class of inflammatory drugs have been tested, in several dosages. Even in human trials, none of the most potent and well-known inflammatory drugs known to man proved beneficial. (Cochrane Database Syst Rev 2000;(2):C0000064; Br Med J 1978 Oct 7;2(6143):994-6; Br Med (Clin Res Ed) 1986 Jan 4;292(6512):21-3; Br Med 3 1976 Dec 11;2(6049):1409-10).

Moreover, a trial with Enlimolab, a drug with putative inflammatory properties even more closely related to the putative mechanism of the current invention, turned out to be detrimental. (Neurology 2001 Oct 23;57(8):1428-34; Neurology 1997; 48 (Suppl): A270).

Applicants note that one of the putative mechanisms of action of the interferon-treatment after H/I related inflammation/stroke is the prevention of neutrophil activation and infiltration. Prior to our experiments, a trial seeking to limit inflammation after stroke in humans by limiting neutrophil activation was stopped prematurely because of futility. (Stroke 2003;34:2543-48).

Thus, one of ordinary skill in the art is confronted with much art that shows that anti-inflammatory drugs are not effective in H/I related inflammation. One of ordinary skill in the art thus would have had no reasonable expectation of success for using IFN-β in that treatment. There is nothing in the art that would suggest that IFN-β would have a better chance than the anti-inflammatory drugs tested.

Applicants also note that even if the effects of H/I related inflammation in different organs are the same, it is does not necessarily follow that IFN type-I will be effective in all organs. By way of example only, as will be discussed below, endothelial cells differ in different parts of an organism. One of ordinary skill in the art would not assume that IFN type-I will react

the same in all organs. Therefore, one of ordinary skill would not assume that IFN type-I would be equally effective in all organs of an organism.

It is therefore respectfully submitted that the use of interferon or functional parts, derivatives, and/or analogues thereof for the treatment of H/I related inflammation is not obvious. It was rather an unlikely choice considering its properties known in the art. Withdrawal of the rejection is thus requested.

4. Claims 1-21 and 35 U.S.C. § 102(b)

Claims 1-21 are rejected on two grounds. First, claims 1-21 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by EP 0 797 998 A1 ("Sano *et al.*"). Specifically, it was asserted that Sano *et al.* teach a method of using type-I interferons, including IFN-β, to treat cardiovascular diseases and/or complications. The types of cardiovascular diseases and/or complications include: brain and heart infarction, ischaemic vascular disorders, blood flow insufficiency, vascular restenosis, and vascular disorders related to inflammatory processes. It was also asserted that Sano *et al.* teach the method may be used to treat necrosis as a result of angitis, which leads to "clot formation" and "aneurysm formation." Applicants respectfully traverse the rejection.

Applicants respectfully submit that Sano *et al.* is directed toward the protection of endothelial cells as a direct effect. The present invention treats H/I related inflammation. Thus, Sano *et al.* is not directed towards the subject matter of the present invention. Sano *et al.* is concerned with the protection of endothelial cells. Endothelial cells can be derived from varying sources. The endothelial cells that Sano *et al.* used in their experiments were umbilical vein endothelial cells. It is not possible to extrapolate results obtained in umbilical cord endothelial cells to cells from other sources. Applicants assert, that it is well known in the art, for example, that umbilical vein endothelium is very different from brain endothelium. Moreover, Sano *et al.* do not show any other data than those derived from the mentioned endothelial cells in culture.

Moreover, the claims recite "administering to an/the individual." Sano *et al.* does not perform "administering to an individual." Sano *et al.* only presents experiments *in vitro*. Sano *et al.* does not describe each and every element of the claims, and therefore does not anticipate the

claims. *See* Verdegaal Brothers v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). It is requested that the Examiner maintain the same standard for enablement for the present invention and the art. The present invention provides *in vivo* data on the effectiveness of IFN-β for the purpose of treating H/I related inflammation. Sano *et al.* presents only *in vitro* data and extrapolates from these results. If the Examiner considers the present invention not enabled over the full *in vivo* scope as result of lack of experimental support, then surely Sano *et al.* cannot be enabled at all.

Claims 1-21 also stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by JP 09151337 ("Sano"). Specifically it was asserted that Sano teaches a method of using IFN-β in the transplantation of organs and to treat various cardiovascular conditions, including restenosis after PTCA, intima hyperplasia after arteriosclerosis, and vasculitis in artery occlusion. It was also asserted that the method taught by Sano would inherently be effective for reducing cell death following H/I because, for example, a method directed to treating restenosis following PTCA would inherently, whether appreciated or not, decrease cell death as a result of treating restenosis. Applicants respectfully traverse the rejection.

Applicants respectfully submit that Sano is concerned with multiplication of smooth muscle cells. Inhibiting multiplication of smooth muscle cells is not an element of the claimed inventions. Additionally, muscle cell proliferation is a process of weeks. The present invention assesses H/I related inflammation. This resistance is observed shortly after removal of the primary cause. H/I related inflammation is a phenomenon of the microvascular system, *i.e.*, of capillary vessels that do not have smooth muscle cells. H/I related inflammation is thus independent of smooth muscle cell proliferation. Administration of interferon in a method of the invention is thus performed for a different part of the vascular system and with a different purpose.

Claims 1-21 are not anticipated by Sano *et al.* or Sano.

Support for new claims 22-24 may be found in paragraphs [0010], [0052], and [0057] of the Specification among other places.

If questions remain after consideration of the foregoing, the Office is kindly requested to

contact applicants' agent at the address or telephone number given herein.

The Amendment mailed September 7, 2005 inadvertently did not show the changes to the claims. This Amendment does. A petition for a one-month extension has been included. A PTO/SB/17 (12-04v2) for Fee Transmittal for FY 2005 was sent with the September 7th Amendment to request debiting of deposit account #20-1469 to pay for the newly added claims. Therefore, a PTO/SB/17 (12-04v2) for Fee Transmittal for FY 2005 was not sent with this Amendment. If any questions should arise, the Office is welcome to contact the contact applicants' agent at the address or telephone number given herein.

Respectfully submitted,

Kelly A. Echols
Registration No. 55,911
Agent for Applicants
TRASKBRITT, P.C.
P.O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: 801-532-1922

Date: September 9, 2005
KAE/bv

Enclosures: Appendix A
Replacement Sheets
Annotated Sheets Showing Changes

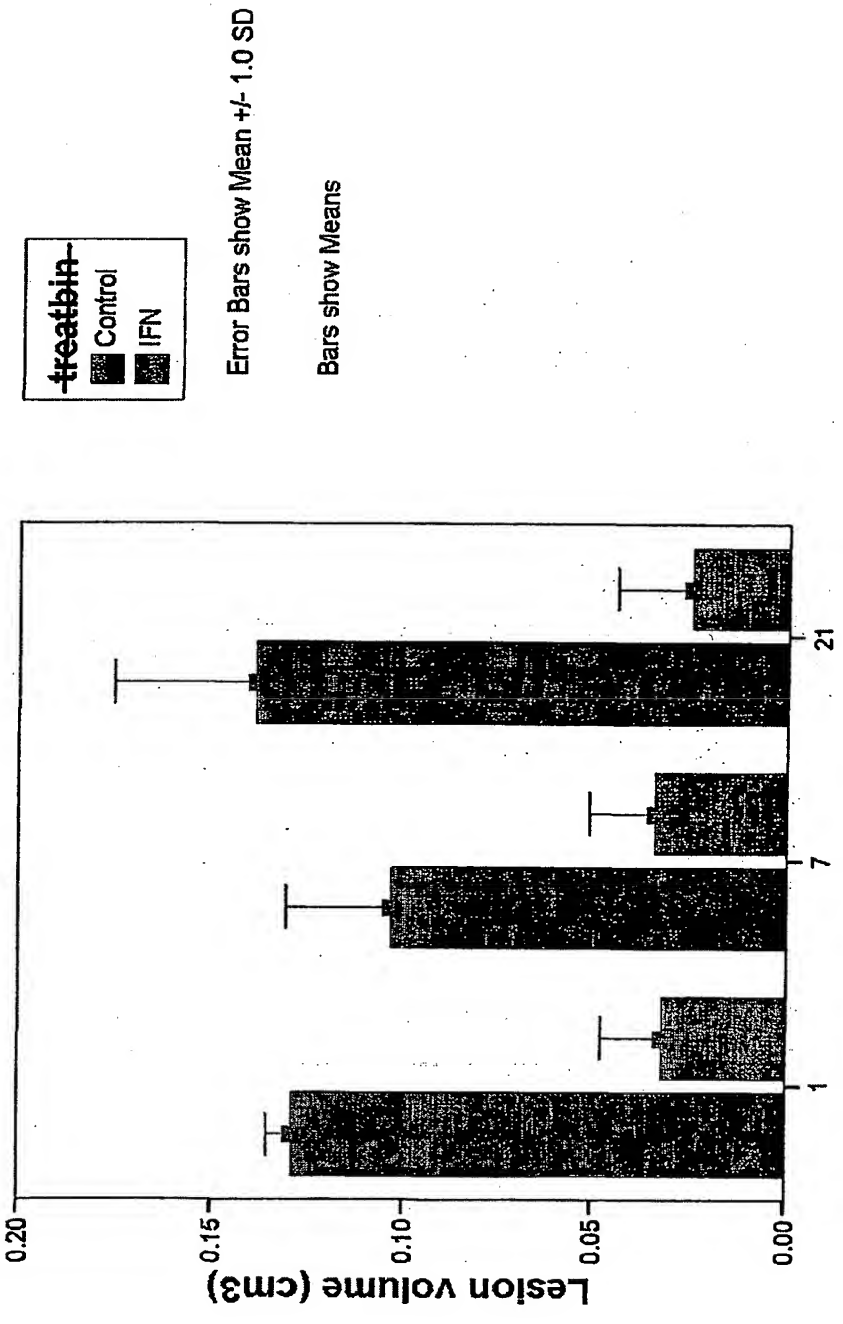

FIG. 4

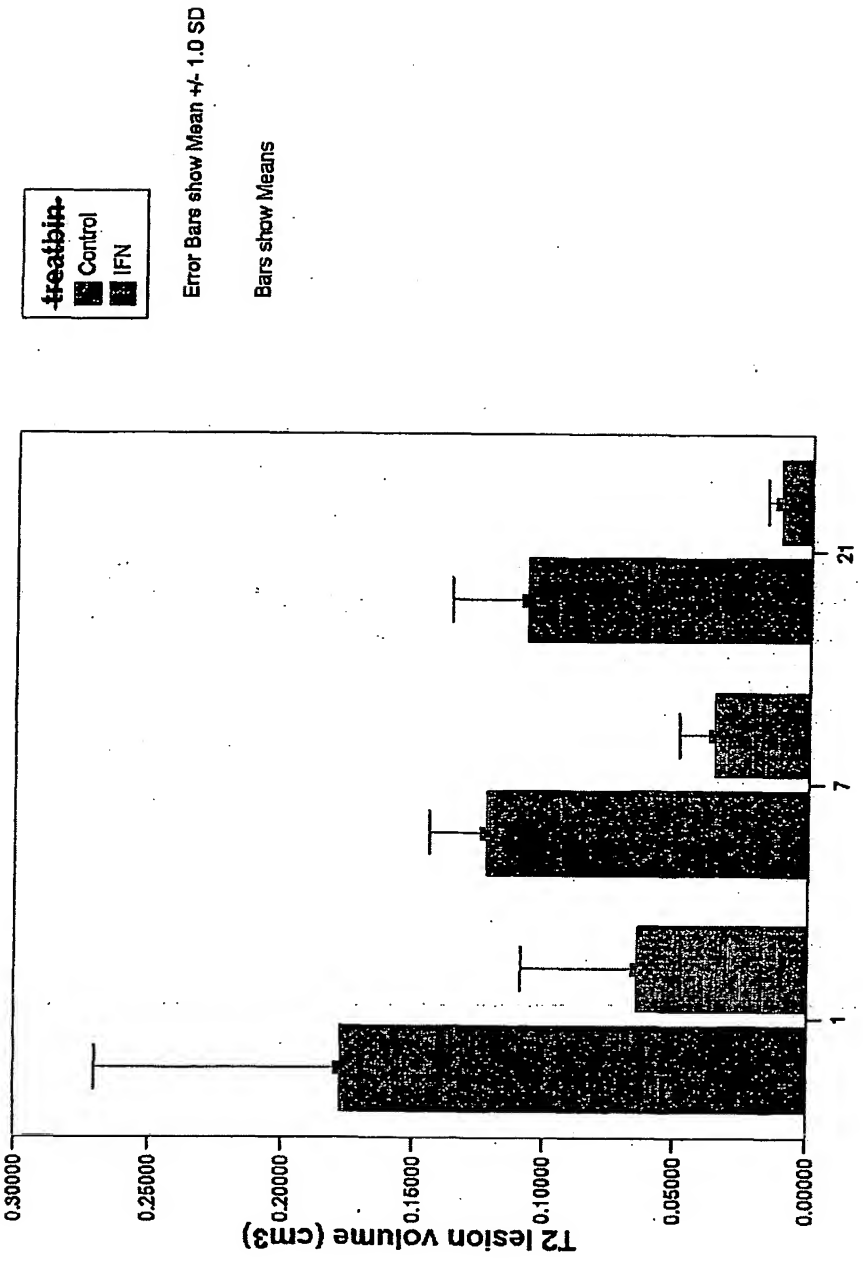

FIG. 8

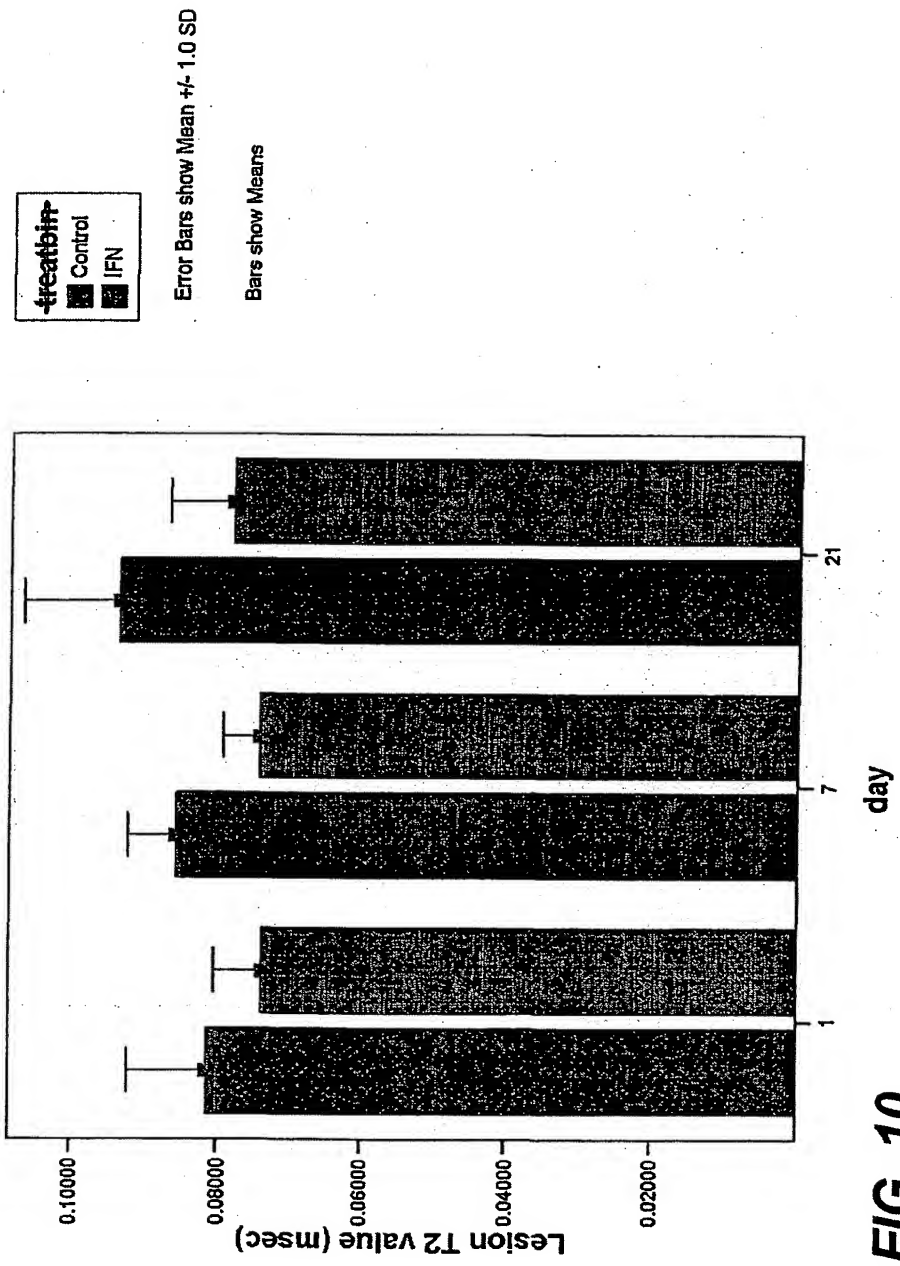

FIG. 10